PB81-109449

# Captan
# Position Document 1

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# CAPTAN: POSITION DOCUMENT 1

OFFICE OF PESTICIDE PROGRAMS

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

U.S. ENVIRONMENTAL PROTECTION AGENCY

EPA/SPRD-80/104

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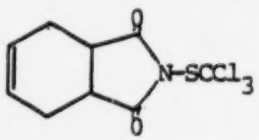
## I. BACKGROUND

### A. Chemical and Physical Characteristics

Captan is the accepted common name for N-trichloromethylthio-4-cyclohexene-1,2-dicarboximide. The chemical is also known by the trade names Merpan, Orthocide, Vondcaptan, Vancide-89 and SR-406. It is in the pesticide classification known as dicarboximides. The pesticide acts as a protectant against fungal infestations, and is used extensively as a fungicide on many food crops and plant seeds. It is also used in several nonagricultural applications.

Physically, captan in pure form is an odorless, white, crystalline substance with a melting point of 178°C. The technical grade material is a pungent, yellow to buff, amorphous powder with a melting point of 160°C to 170°C. Its specific gravity is 1.62 as technical grade product and 1.73 in its pure form. The pure substance has a vapor pressure of less than $1 \times 10^{-5}$ mm Hg at 25°C. It is moderately soluble in many organic solvents including chloroform, benzene and dioxane but practically insoluble (i.e., <0.5 ppm) in water at room temperature. The molecular weight is 300.57 and the empirical formula is $C_9H_8Cl_3NO_2S$. Its structural formula is:




### B. Registered Uses

#### 1. General

Captan was first patented in 1951 by the Standard Oil Development Company (Patent Number 2,553,771). The company again patented the chemical in 1953 (Patent Number 2,653,155). In 1955 Esso was also issued a patent (2,713,058).

There are approximately 600 federally-registered pesticide products containing captan as an active ingredient. These registrations are held by 139 registrants. No federally

registered products contain captan as an inert ingredient. There are approximately 100 applications pending for federal registration of state-registered products containing captan as an active ingredient.[1/] In accordance with Section 24(c) of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), 33 additional captan products have been registered in states that have demonstrated that those products are necessary to meet special local needs.

Captan is used as a fungicide: 1) on a wide variety of fruit, vegetable and ornamental crops, some of which are grown on home and garden sites; 2) on numerous plant seeds; 3) on food crop packing boxes; 4) in soil preplanting treatment; 5) on surfaces inside and outside the home; 6) in cosmetics and pharmaceuticals, oil based paints, lacquers, paper, wallpaper paste, plasticizers, polyethylene, vinyl, rubber stabilizer and textiles; 7) in combination with insecticides on food crops, seed treatment and household pets. Pesticide products containing captan are most widely used as wettable powders (50-80% captan) and dusts (7.5-15% captan). Other formulations are commercially available including 4-pound per gallon aqueous suspensions and coated granules.

2. Tolerances

EPA has established tolerances, for captan residues (40 CFR 180.103) in or on these raw agricultural commodities:

a. Tolerances for Preharvest, Postharvest or Combination Uses:

1) 100 ppm (parts per million) - beet greens, cherries, lettuce, spinach;

2) 50 ppm - apricots, celery, grapes, leeks, mangoes, nectarines, green onions, peaches, plums (fresh prunes), shallots;

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1/ Pesticide products formerly registered under state pesticide registration laws and shipped or distributed for sale solely within intrastate commerce are subject to federal pesticide regulations under FIFRA section 3(a) and 40 CFR Section 162.17(a). Many registrants who had state-registered products have established the intent to obtain federal registration for intrastate use of these products.

3) 25 ppm - apples, avocados, blackberries, blueberries (huckleberries), cantaloupes, crabapples, cranberries, cucumber, dewberries, eggplants, garlic, honeydew melons, muskmelons, dry bulb onions, pears, peppers, pimentos, pumpkins, quinces, raspberries, rhubarb, strawberries, summer squash, tomatoes, watermelons, wintersquash;

4) 2 ppm - beet roots, broccoli, brussels sprouts, cabbage, carrots, cauliflower, collards, cottonseed, kale, mustard greens, peas, rutabaga roots, soybeans, sweet corn, turnip greens and roots;

5) 0.25 ppm - taro

b. Tolerances for the transmission of captan residues to meat, milk, and eggs from feeding cattle or poultry with the following captan-treated commodities or their by-products are:

1) 100 ppm - almond hulls;

2) 25 ppm - beans, grapefruit, lemons, limes, oranges, pineapple, potatoes, tangerines;

3) 2 ppm - almonds

3. Production

Section 7(c) of FIFRA requires manufacturers and formulators to submit information to EPA on the production, sale, and distribution of pesticide products. This information is confidential and may not be made available to the public under Sections 7(d) and 10 of FIFRA. However, a confidential memorandum summarizing this information (Williams, 1980) has been sent to the Deputy Assistant Administrator for Pesticide Programs.

4. Usage Data

The agricultural usage data as presented in Table 1 indicate that between 8.5 and 9.7 million pounds of captan were used annually during 1978 and 1979. The nonagricultural (industrial) usage data estimated by the Agency are indicated in Table 2.

Table 1

PRELIMINARY QUANTITATIVE USAGE OF CAPTAN IN THE UNITED STATES AGRICULTURE
(1978 - 1979)

| Crop Site[1] | Application | Units Treated/ Year[2] | Application Rate/ Treatment[3] (pounds a.i.) | Treatments/ Year[4] | Quantity a.i./ Applied[5] (in thousands of pounds) | Percent Crop or Site Treated/ Year[6] |
|---|---|---|---|---|---|---|
| Pome Fruits | | | | | | |
| Apples | foliage & fruit | 165,000 - 168,000 acres | 2-4/acre | 4-6 | 2,475 - 2,520 | 31.7 - 32.3 |
| Pears | foliage & fruit | 1,900 - 5,500 acres | 3/acre | 3-4 | 20 - 58 | 1.9 - 5.5 |
| Stone Fruits | | | | | | |
| Cherries | foliage & fruit | 6,400 - 17,200 acres | 3/acre | 3 | 58 - 155 | 5.1 - 13.8 |
| Peaches/ Nectarines Apricots | foliage & fruit | 73,000 - 84,000 acres | 3/acre | 3 | 657 - 756 | 18.2 - 21.0 |
| Plums/ Prunes | foliage & fruit | 10,000 - 26,000 acres | 3/acre | 2 | 60 - 156 | 6.7 - 17.3 |
| Other Fruits and Nuts | | | | | | |
| Almonds | foliage & fruit | 129,000 - 154,000 acres | 4/acre | 1-2 | 774 - 924 | 35.8 - 42.8 |
| Grapes | foliage & fruit | 207,000 - 216,000 acres | 1.5/acre | 2 | 621 - 648 | 29.6 - 30.9 |
| Lemons/ Limes | skirt treatment | 7,000 - 9,000 acres | 14/acre | 1 | 98 - 126 | 7.1 - 9.1 |
| Strawberries | foliage & fruit | 35,000 - 39,000 | 2/acre | 2-4 | 210 - 234 | 97.2 - 100.0 |

Table 1 (Continued)

PRELIMINARY QUANTITATIVE USAGE OF CAPTAN IN THE UNITED STATES
AGRICULTURE
(1978 - 1979)

| Crop Site[1] | Application | Units Treated/ Year[2] | Application Rate/ Treatment[3] (pounds a.i.) | Treatments/ Year[4] | Quantity a.i./ Applied[5] (in thousands of pounds) | Percent Crop or Site Treated/ Year[6] |
|---|---|---|---|---|---|---|
| **Seed Treatments** | | | | | | |
| Corn (field) | seed treatment | 1.95 - 1.97 billion lbs. seed | .875 - .938 oz. a.i./ 100 lb. seed | 1 | 1,102 - 1,114 | 100% of seed and planted acres |
| Corn (sweet) | seed treatment | 9.2 million lbs. seed | .175 - 0.2 oz. a.i./ 100 lb. seed | 1 | 1 - 1.2 | 100% of seed and planted acres |
| Cotton | seed treatment | 273.6 - 276.0 million lbs. seed (plants 10.5 - 10.6 million acres) | 2 oz. a.i./ 100 lb. seed | 1 | 342 - 345 | 80.0 - 80.8% of seed and planted acres |
| Potatoes | seed treatment | 589,000 - 810,000 acres | 1.37/acre | 1 | 807 - 1,110 | 48.3 - 66.4% |
| All Other Field Crops | seed treatment | 7/ | 7/ | 7/ | 690 - 725 | 7/ |
| All Other Vegetables | seed treatment | 7/ | 7/ | 7/ | 286 - 330 | 7/ |

Table 1 (Continued)

PRELIMINARY QUANTITATIVE USAGE OF CAPTAN IN THE UNITED STATES AGRICULTURE
(1978 - 1979)

| Crop Site[1] | Application | Units Treated/ Year[2] | Application Rate/ Treatment[3] (pounds a.i.) | Treatments/ Year[4] | Quantity a.i./ Applied[5] (in thousands of pounds) | Percent Crop or Site Treated/ Year[6] |
|---|---|---|---|---|---|---|
| Vegetables | | | | | | |
| Lettuce | foliage | 13,000 - 53,000 acres | 1.5/acre | 1 | 20 - 80 | 28.7 - 84.5 |
| Tomatoes | foliage & fruit | 7,000 - 17,000 acres | 3/acre | 2 | 42 - 102 | 29.3 - 71.1 |
| Other Vegetables | foliage & fruit | 7/ | 7/ | 7/ | 35 - 84 | 7/ |
| Commercial Greenhouses and Ornamentals | 7/ | 7/ | 7/ | 7/ | 45 - 50 | 7/ |
| All Other Agricultural Uses (including post-harvest) | 7/ | 7/ | 7/ | 7/ | 45 - 50 | 7/ |
| Home and Garden | 7/ | 7/ | 7/ | 7/ | 106 - 160 | 7/ |
| Total | | | | | 8,494 - 9,728 | |

Table 1 (Continued)

PRELIMINARY QUANTITATIVE USAGE OF CAPTAN IN THE UNITED STATES
AGRICULTURE
(1970 - 1979)

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1/ The crops/sites presented are those for which usage data are readily available. All fruit, nut and vegetable data are for preharvest use.

2/ Units treated represent annual averages based on available data. Ranges are given for those cases where usage figures are most variable. All units can be expected to vary considerably by year due to changes in incidence and severity of disease problems. Usage estimates may change once detailed crop/site data are gathered and analyses completed.

3/ Rates are average values based on one or more of the following: registration data, product labels, usage data, state recommendations.

4/ Number of applications based primarily on usage data indicating incidence of retreatment.

5/ Estimates derived based on application rates, units treated and number of treatments.

6/ Estimates based on units treated per year and acres grown or estimated quantities of seed (corn, cotton) required to plant acres grown. Estimates can be expected to change once detailed crop/site analyses are completed.

7/ Available data can not be reliably broken into more specific site estimates.

8/ See Table 4.

Sources: Chevron Chemical Co., Rohm and Haas Co., Stauffer Chemical Co. and labels from federally registered pesticide products.

Table 2

Captan Use on Non-Agricultural Sites 1/

| Site | Estimated Annual Usage Level (pounds a.i.) | | | | Products |
|---|---|---|---|---|---|
| | <1,000 | 1,000-10,000 | 10,000-50,000 | 50,000-150,000 | |
| paste | | | | x | principally wallpaper |
| paint | | | x | | paints for greenhouses, medical facilities, food packing plants, etc. |
| textiles | | | | x | vinyl-coated fabrics (mattresses, mats, curtains, etc.) |
| vinyl | [usage included in textiles] | | | | above uses plus auto vinyl roofs, astroturf, others |
| lacquers | x | | | | very limited |
| paper | x | | | | " |
| rubber stabilizers | x | | | | " |
| plasticizers | | x | | | plastic additive |
| polyethylene | | x | | | garbage bags, pond liners |
| vinyl resins | | x | | | vinyl precursor |
| packing boxes | undetermined | | | | |
| wood | little or none | | | | |
| surface sprays | little or none | | | | mildew control spray additive |

1/ Captan is used to some extent in cosmetics, however usage estimates are not available.

Source: EPA estimates based on a telephone survey of product manufacturers (Fall 1979) and data available from industry studies.

## II. REGULATORY HISTORY

### A. USDA Actions

A joint U.S. Department of Agriculture–Department of Health, Education and Welfare statement was published in the Federal Register of April 13, 1966, for implementation of a National Research Council recommendation that "The concepts of 'no residue' and 'zero tolerance' as employed in the registration and regulation of pesticides are scientifically and administratively untenable and should be abandoned" (FR 1966). The joint statement specified that registrations of all uses involving a reasonable expectation of small residues on food or feed at harvest should be discontinued as of December 31, 1967 unless data were presented to support a finite tolerance or exemption from a tolerance. Since no such evidence had been provided for the use of captan on gooseberries, cancellation of this use was proposed.

The USDA Pesticide Regulation Division (PRD), issued several regulatory notices from January 10, 1968 to November 22, 1971 concerning safety studies, nonfood use restrictions, cancellation of uses based on "no residue" or "zero tolerances," and one product cancellation.

The PR Notice 68-3 of January 10, 1968 to Manufacturers, Formulators, Distributors and Registrants of Economic Poisons announced that captan uses for seed treatments were classified as nonfood uses (USDA 1968). Therefore, registration of products for these uses was continued in the absence of finite tolerances.

PR Notice 68-5 of January 30, 1968 concerned "no residue" and "zero tolerance" registrations beyond December 31, 1967 (USDA 1968a). This was an extension of registration for uses of captan on asparagus, gooseberries and packing boxes until January 1, 1969. However, the PR Notice 68-8 of April 24, 1968 classified the uses of captan on asparagus and packing boxes as nonfood uses (USDA 1968b). The uses were therefore continued in the absence of data supporting finite tolerances.

PR Notice 69-4, of February 1, 1969, announced that since no evidence was provided to support a finite tolerance of captan on gooseberries the use was cancelled (USDA 1969).

PR Notice 70-8 of March 10, 1970 requested registrants to undertake the additional safety studies necessary to further evaluate captan concerning its carcinogenic and teratogenic potential (USDA 1970). Such tests were to include negative and positive controls. Epidemiological data were also requested for persons with a known history of high exposure to captan.

The PRD cancelled the registration of Vancide 89RE on November 22, 1971. This was a technical grade product for manufacturing and formulating use. The cancellation action was taken pursuant to Section 4(c) of FIFRA (now superceded by FIFRA Section 6(b) as amended in 1978) due to the registrant's lack of response to the January 8, 1971 notice of intent to cancel.

B. Other Agency Reviews and Findings

The Report of the Secretary's Commission on Pesticides and Their Relationship to Environmental Health by the U.S. Department of Health Education and Welfare, reviewed the significance of adverse effects data on a number of pesticides, including captan (Mrak et al., 1969).

The Commission recommended unanimously that human exposure to captan be considered a potential health hazard. The following were among the Commission's findings relating to captan:

1) it was reported as a cause of dermatitis from apple spraying and allergic dermatitis was demonstrated in agricultural workers;

2) it produced mutagenic effects in bacteria, human embryonic lung cells and cell lines derived from the kidney of the kangaroo rat;

3) it induced teratogenic effects in developing chicken embryos; and

4) it increased tumor incidence in mice, with a significance level of $p = 0.02$.

The Commission specifically recommended: 1) reducing exposure of the general population from dietary sources of captan pending the completion and evaluation of additional testing of tumorigenicity; 2) minimizing workers' exposure to captan pending completion of safety studies; 3) giving high priority to captan in a testing program for mutagenesis; and 4) restricting captan immediately should it be found to be teratogenic.

Summary results of a National Cancer Institute bioassay of captan for possible carcinogenicity in rats and mice were published in the Federal Register (FR 1977). Tumors in the duodenum of mice were associated with captan treatment. There was no convincing evidence that tumors observed in rats were related to captan treatment.

C. Other Regulatory Actions

The United States Department of Labor, Wage and Hour Division, published final rules pertaining to captan in the Federal Register (FR 1979). The notice indicated that while current regulations provided for the issuance of waivers permitting employment of 10- and 11-year old minors in hand harvesting of short-season crops, because

captan was a suspected carcinogen, no waiver could be issued for minors to harvest captan-treated crops of strawberries or potatoes.

The Environmental Protection Agency's Office of Water Planning and Standards (OWPS) on February 16, 1979 published amendments to the final rule designating captan as a hazardous substance (FR 1979). This action was taken in accordance with the Clean Water Act (CWA) for the control of the discharge of hazardous substances. The OWPS also required that all facilities discharging 10 pounds or more of captan to waters or shoreline report that fact in accordance with Section 311 of CWA. Further, facilities which discharge captan are regulated by CWA Sections 309 and 402 and are required to comply with National Pollutant Discharge Elimination System Permit regulations.

Under 21 CFR 176.170 the FDA has established regulations concerning captan as a component of coatings for paper or paperboard surfaces that contact food. The chemical may be used as a mold- and mildew-proofing agent in such coatings. The amount of captan permitted as a component of the coatings depends on the particular type of food which will contact it. The permissible concentration of captan is established by a determination of the amount of the chemical that can be extracted with certain solvents under certain conditions.

Following an adverse inspection report from the Food & Drug Administration concerning the laboratory testing practices of Industrial Bio-test Laboratories (IBT), the EPA Deputy Assistant Administrator for Pesticide Programs notified all registrants that studies conducted by IBT and used in support of their pesticide registrations must be audited (Johnson, 1977 and 1978). There were 12 such audits completed on May 15, 1979 by registrants of products containing captan. The audits disclosed a large number of IBT testing deficiencies and resulted in the Agency's determination that none of the 12 studies were valid (Auerbach, 1980).

## III. SUMMARY OF SCIENTIFIC EVIDENCE TO SUPPORT REBUTTABLE PRESUMPTION

### A. Oncogenicity

40 CFR Section 162.11(a)(3)(ii)(A) provides that "a rebuttable presumption shall arise [that a notice of intent to cancel registration shall be issued] if a pesticide's ingredient(s), metabolite(s), or degradation product(a)... induces oncogenic effects in experimental mammalian species or in man as a result of oral, inhalation, or dermal exposure..." Section 162.3(bb) defines the term oncogenic as "the property of a substance or mixture of substances to produce or induce benign or malignant tumor formation in living animals."

The Agency has concluded that all pesticide products containing captan exceed the chronic risk criterion relating to oncogenicity. This finding is based on the studies presented below. In summary, significantly elevated incidences of intestinal and liver tumors were observed in male mice following 20-month and 18-month oral administrations of captan, respectively. Two long-term rat studies resulted in no significantly increased levels of tumors. One rat study and one mouse study were determined to be invalid and therefore cannot be used in evaluation of captan.

Gulf South Research Institute conducted a bioassay for the National Cancer Institute (NCI, 1977) utilizing B6C3F1 mice and Osborn-Mendel rats. The mouse treatment groups consisted of 50 male and 50 female mice per dose level with 10 matched controls per sex. A pooled control group was formed using the matched controls and an additional 70 control animals per sex from other studies being conducted at that time. Captan, at 8,000 and 16,000 ppm, was administered to 35-day-old mice in their diet for 80 weeks. The mice were sacrificed after 11 additional weeks on a control diet. A dose-related increase in the incidence of duodenal tumors (adenomatous polyps and polypoid carcinomas) was seen in both males (pooled controls 0/63, low dose 1/43, high dose 3/46, $p = 0.033$) and females (pooled controls 0/68, low dose 0/49, high dose 3/48, $p = 0.022$). The rarity of these lesions in this particular strain of mice increases the likelihood that the lesions were caused by the administration of captan. Decreased incidences of hepatomas and lung tumors were also noted in the results of this study. However these observations do not obviate the Agency's concern about the increased duodenal tumors.

Preliminary results from a registrant sponsored (Stauffer Chemical Co. and Chevron Chemical Co.) 2-year mouse study appear to confirm an increased incidence of duodenal tumors among captan-treated mice. However, the Agency has not scientifically evaluated these data or made any conclusions concerning such results (Incomplete Study-Not Referenced).

Innes et al., 1969, administered captan daily to groups of B6C3F2 and B6AKF1 mice. Eighteen males and 18 females were used for each strain, at a dose of 215 mg/kg/day by gavage from the 7th day of age to the 28th day. From the 28th day to the end of the study, captan was administered in the diet at 560 ppm. These same authors reported an increased incidence of hepatomas in males only ($p<0.05$) (Bionetics, 1968). A reanalysis of the data in the Mrak report (1969) using the Mantel-Haenzel method gave a significance level at $p<0.02$ for the hepatomas in males. The tumor incidence among captan-treated females was not significantly elevated. The ability of this study to detect increased tumors was poor, however, since the number of animals was too small, it continued only 18 months, and only one dose level was used (much lower than that in the 1977 NCI mouse study).

The NCI (1977) rat study treatment groups consisted of 50 animals of each sex per dose level and 10 matched controls per sex. An additional 65 animals per sex were used for a pooled control group. The 35-day-old rats were given 8,000 or 16,000 ppm captan in their diet. The high dose level proved to be too toxic and the group was dropped from the study at 18 weeks. A new low dose group was started at 4000 ppm. Twenty-one weeks later the dosage of both groups was halved, resulting in time-weighted average doses of 2,525 and 6,050 ppm for the 80 weeks of treatment. The rats were sacrificed after an additional 33 weeks. No lesions were seen which could be attributed to captan, however the authors reported that: "In rats a positive dose-related trend and a difference between incidences of tumors in high-dose and pooled-control groups were found in females when the data for adrenal cortical adenoma were combined with those for adrenal cortical carcinoma (pooled controls 0/64, low-dose 2/50, high-dose 3/47, $p=0.047$). There was also a positive dose-related trend for the incidence of C-cell adenoma of the thyroid in female rats (pooled controls 1/66, low-dose 1/49, high dose 4/44, $p = 0.0035$)."

A study by Hazelton Laboratories (1956) used even fewer animals (10 male and 10 female rats per group) for a 2-year captan feeding study. Substantial mortality occured in many of the groups, including 50% of the control males and 40% of the control females. The high dose group (10,000 ppm) was sacrificed at only 55 weeks, which was insufficient time for tumor development. The medium and low dose groups (5000 and 1000 ppm) were sacrificed at 104 weeks. No tumors that could be associated with captan were seen; however, the ability of this study to detect tumors was very poor due to the small sample size and short term of the high dose testing.

A 15-month mouse study (IBT B9271) and a 2-year rat study (IBT B9267) have been judged invalid by a joint US/Canadian governmental audit (Auerbach, 1980).

B. Mutagenicity

40 CFR Section 162.11(a)(3)(ii)(A) states that "a rebuttable presumption shall arise [that a notice of intent to cancel registration shall be issued] if a pesticide's ingredient(s), metabolite(s), or degradation product(s)... induces mutagenic effects, as determined by multitest evidence." Section 162.3(y) defines mutagenicity as "the property of a substance or mixture of substances to induce changes in the genetic complement of either somatic or germinal tissue in subsequent generations." Section 162.3(l) defines degradation product as "a substance resulting from the transformation of a pesticide by physiochemical or biochemical means."

Human exposure to a mutagen has serious implications. The possible adverse effects to people, especially those of reproductive age, are spontaneous abortions, stillbirths, birth defects in their children, and diseases in the adult life of subsequent generations. Any of these effects could result from exposure of the male and/or female parent to a mutagen. In addition, those exposed can be adversely affected by mutations of the somatic cells.

The primary objective of mutagen testing is to determine whether a chemical has the potential to cause heritable genetic alterations in man. Direct methods for this assessment do not exist. As a consequence, non-human and even non-mammalian tests have been utilized in efforts toward this assessment (DHEW, 1977).

Evidence in both prokaryotic (i.e. bacterial) and eukaryotic (i.e. mammalian) systems indicates that captan is a point (gene) mutagen. This means that captan can interact with DNA of several species to produce mutations in both reproductive and other body cells. There is also evidence that captan can induce chromosomal aberrations in somatic cells of mammals. In addition, available data indicate that captan can damage DNA of both prokaryotic and eukaryotic organisms.

Though not all of the available mutagenicity data are presented in this document, the following representative data support the Agency's conclusion that captan is capable of inducing gene mutations, DNA damage and chromosomal aberrations and therefore meets this risk critrion. Additional mutagenicity data are being sought primarily through registrant compliance with FIFRA Section 3(c)(2)(b) requests (Johnson, 1980).

1. Gene Mutations [Data Summarized in Table 3]

Gene (point) mutations are alterations which affect single genes. These alterations include base pair substitutions and frameshift mutations as well as other small deletions and insertions. Applicable *in vitro* test systems include both forward and reverse mutations assays in bacteria, yeast, fungi,

Table 1

GENE MUTATION: BACTERIA

| Reference | Test | Organism | Results | Comments |
|---|---|---|---|---|
| Bridges et al., 1973 | forward mutation | Escherichia coli | + | No metabolic activation |
| Bridges et al., 1972 | reverse mutation spot test | E. coli | + | No metabolic activation |
| Buselmaier et al., 1972 | mouse host-mediated reverse mutation | Salmonella typhimurium G46<br>Serratia marcescens | +<br>+ | 500 mg/kg captan injected intra peritoneal |
| Ficsor et al., 1977 | Reverse mutation: mouse host-mediated | S. typhimurium G46 | - | 1,000 mg/kg orally 3 subcutaneous injections 2,000 mg/kg orally of 500 mg/kg |
| | rat host-mediated | S. typhimurium TA 1950 | - | |
| | in vivo mouse blood - urine mediated | S. typhimurium G46 | - | urine mediated |
| | in vivo rat-blood-mediated | S. typhimurium TA 1950 | - | |
| | in vivo reverse mutations assays: | | | |
| | captan + saline | S. typhimurium TA 1950 | + | |
| | captan + rat blood | S. typhimurium TA 1950 | - (decreased) | |
| | captan + rat plasma | S. typhimurium TA 1950 | + | |
| | captan + human blood | S. typhimurium TA 1950 | - (decreased) | |
| | captan + S-9 rat liver microsome fraction | S. typhimurium TA 100 | + | revertants/plate 367 without S-9 109 with S-9 |
| Ficsor et al., 1978 | reverse mutation | S. typhimurium G46 TA 1530, TA 1950, TA 100 | + | Used as positive control in spot and liver suspension assays. S-9 metabolic activation system with TA 100 reduced the mutagenicity |

Table 3 (Continued)

GENE MUTATION: BACTERIA

| Reference | Test | Organism | Results | Comments |
|---|---|---|---|---|
| Gabridge and Legator, 1969 | Mouse host-mediated reverse mutation spot test | S. typhimurium G 46 | -<br>- | Too few organisms recovered - not well described. |
| Legator et al., 1969 | Reverse mutation spot test | E. coli | + | |
| Marshall et al., 1976 | Reverse mutation plate test | S. typhimurium TA 1535, | + | Approximately 1/2 as mutagenic after metabolic activation. |
| McCann et al., 1975 | Reverse mutation spot test | S. typhimurium TA 1538 | - | No metabolic activation used |
| | | S. typhimurium TA 1535 TA 100, TA 98 | + | |
| Nagy et al., 1975 | Reverse mutation spot test | E. coli WP 2 try-hcr+ | + | "strong mutagen". |
| | | E. coli WP 2 try-hcr- | + | " " |
| Seiler, 1975 | Reverse mutation spot test | S. typhimurium TA 1535 | Inconclusive | Protocol and results not adequately described. |
| Shirasu et al., 1976 | Reverse mutation spot test | E. coli WP 2 try-hcr+ | + | |
| | | E. coli WP 2 try-hcr- | + | |
| | | S. typhimurium TA 1535 | + | |
| | | S. typhimurium TA 1536 TA 1537, TA 1538 | - | |

Table 3 (Continued)

GENE MUTATION: BACTERIA

| Reference | Test | Organism | Results | Comments |
|---|---|---|---|---|
| Simmon et al., 1977 | Reverse mutation plate test | E. coli WP 2 uvr A- | + | |
| | | S. typhimurium TA 1535, TA 100 | + | Base pair substitution. |
| | | S. typhimurium TA 1537, TA 1538 | | |
| Szybalski, 1958 | Reverse mutation spot | E. coli Sd - 4 | Inconclusive | No sufficient information to evaluate. |

GENE MUTATION: EUKARYOTIC MICROORGANISMS

| Reference | Assay | Organism | Results | Comments |
|---|---|---|---|---|
| Bignami et al., 1977 | Point mutation | Aspergillus nidulans | + | No metabolic activations used. |

GENE MUTATIONS: MAMMALIAN CELLS IN CULTURE

| | | | | |
|---|---|---|---|---|
| Arlett et al., 1975 | Ouabain resistance induction | Chinese hamster SAG suspension indefinite treatment | | |
| | | Ouabain, suspension treatment: lung fibroblast SAG and Ouabain, vapor treatment cells | + | |
| | | | + | |

and mammalian cells in culture. The lower prokaryotic (e.g., bacteria) systems detect only point mutations, while higher eukaryotic systems detect multi-locus deletions as well.

The information available as given below on the mutagenicity of captan has shown that it can cause gene mutations in bacteria, in eukaryotic microorganisms and mammalian cells in culture.

a. Bacteria

As an example of bacterial testing to indicate mutagenicity, many mutants have been isolated which block various steps in histidine biosynthetic pathways of Salmonella typhimurium. Among these mutants, a series of tester strains have been used in testing captan which revert by specific mechanisms, e.g., base-pair substitution or frameshift mutations (DHEW, 1977).

Captan has been demonstrated to produce reverse mutations in Salmonella typhimurium G46, TA 1535, TA 100, and TA 1950 (Ficsor et al., 1977; Ficsor et al., 1978; Marshall et al., 1976; McCann et al., 1975; Shirasu et al., 1976; and Simmon et al., 1977). Marshall et al., (1976) found a mutagenic response in a plate test with S. typhimurium TA 1537. However, Shirasu, et al. (1976) and Simmon et al. (1977) observed no response with this strain. Reverse mutations were also induced in the very sensitive frameshift mutant TA 98 (McCann et al., 1975). Captan appears to be more active, however, in base pair than in frameshift mutation.

Escherichia coli WP 2 has been shown to be susceptible to the mutagenic action of captan. This tryptophan auxotroph was reverted to non-dependence on tryptophan by captan (Nagy et al., 1975; Shirasu et al., 1976; and Simmon et al., 1977).

Bridges et al. (1973), found that captan caused a forward mutation to colicin E 2 resistance in E. coli WP 2 uvr A-. A streptomycin dependent strain (SA4-73) and a thymine dependent strain were shown to revert to streptomycin independence and thymine independence (Legator et al., 1969). This effect demonstrated that captan can cause point mutational changes in these strains.

A spot test using various strains of E. coli WP 2 was designed to detect volatile mutagenic components of captan (Bridges et al., 1972). Captan impregnated filter paper was placed on the agar surface or on the lid of the petri dish. Approximately equal numbers of mutants were observed in each case, indicating that most of the effect of

captan was mediated by a volatile mutagen. The frequency of mutation was increased as the buffer pH increased from 5 to 9 on the filter paper on the lid. The vapor phase mutagen was also demonstrated to be short-lived.

Fewer survivors were observed with an ExrA- strain than with an ExrA+ strain when the captan impregnated filter pad was applied to the agar, but not when it was applied to the lid and not in contact with the agar. This indicates that there is a second mutagenic (diffusible) component of captan causing repairable DNA damage. The diffusible component causing the effect was not identified.

b. Bacteria with Metabolic Activation

A number of systems have been developed to simulate the metabolic capabilities of intact mammals. The various metabolic activation systems used can be grouped into three main categories: (1) Whole animals are employed to activate the test chemical. The systems most commonly used are the host-mediated assay and the analysis of body fluids for the presence of mutagens. (2) Certain strains of mammalian cells in culture are capable of metabolizing chemicals. These are used as feeder cells for the indicator cells which do not have such metabolizing capabilities. (3) Organ homogenates from mammals are used to metabolize chemicals in an in vitro system in the presence of the indicator organism (DHEW, 1977). These bacterial assays employ an exogenous source of metabolic activation in the form of a mammalian liver microsomal preparation. The majority of genetic toxicants must be converted into reactive forms before their effects can be detected.

S-9 liver microsome fractions generally seem to decrease the mutagenicity of captan in microbial assays. Whole blood, but not plasma, also decreases the activity in bacterial systems.

Ficsor et al., (1977) examined the mutagenic activity of captan on S. typhimurium TA 100 after incubation with a rat S-9 microsomal fraction and found an approximately 33% reduction in mutagenic activity over the untreated captan assay. Rat S-9 microsomal fraction decreased the mutagenicity of captan by approximately 50% in S. typhimurium strains TA 1535 and TA 1537 (Marshall et al., 1976). Decrease in mutagenic activity after treatment of captan with S-9 microsomal fraction was also noted in S. typhimurium strains TA 100 and TA 1535 by Simmon et al., (1977).

c. Host-and Fluid-Mediated Bacterial Systems.

Host-Mediated Assay In the host-mediated assay, the indicator organism is introduced into the peritioneal cavity or injected into the circulatory system or the testes of the host mammal. The host is then treated with the substance under test, sacrificed, and the test organism removed and examined for mutation induction. A wide range of cellular systems have been used as indicator organisms: Salmonella, E. coli, Saccharomyces, Neurospora, mouse lymphoma cells, Chinese hamster cells, mouse ascites cells and human lymphocytes.

Fluid-Mediated Assay . After chemicals are metabolized in an animal, they may be excreted in the urine as breakdown products and/or conjugates of the original substance. Microbial indicators have proven useful for the detection of active mutagens in the urine of animals treated with non-mutagenic precursor substances (DHEW, 1977).

S. typhimurium G46 his- and Serratia marcescens a21 leu were injected intraperitoneally in NMRI mice previously injected subcutaneously with 500 mg/kg captan (Buselmaier et al., 1972). After 3 hours, the bacteria were recovered and examined for reverse mutations. Mutagenic responses were seen for both organisms.

Ficsor et al., (1977) performed several host- and fluid-mediated assays with captan using strains of S. typhimurium . Four host-mediated assays were performed as described below. None of them evidenced any increase in mutagenic activity attributable to captan. (1) Upjohn strain Suris albino male mice were injected intraperitoneally with strain G46. One group was given captan orally at 1,000 mg/kg and another group was given 500 mg/kg captan subcutaneously at 0, 60, and 120 minutes after injection of the bacteria. The bacteria were recovered and examined for revertants. (2) Sprague-Dawley male rats were injected intraperitoneally with strain TA 1950 and given 2,000 mg/kg captan orally. The bacteria were recovered after two hours and examined for revertants. (3) A spot assay with strain G 46 was performed using filter discs dipped in blood or urine from mice treated orally with 250 mg/kg captan. (4) Spot assays with strain TA 1950 were performed by placing 3 drops of blood from rats (after oral or intraperitoneal captan treatments)on the assay agar. Quantitative determinations were performed by incubating blood from each sample with strain TA 1950 before plating.

Fluid-mediated assays were performed with strain TA 1950 using human blood, rat blood, plasma, and saline. When captan was incubated in rat blood, the mutagenicity of

captan was inactivated at 500 and 1,000 ug/ml captan, but not at 5,000 and 10,000 ug/ml. Captan was mutagenic in saline, in the absence of rat blood. Rat plasma was inactivated by 20 ug/ml captan, but not 200 ug/ml. The researchers reported that this inactivation could be attributed to captan's reaction with glutathione localized in red blood cells. Human blood inactivated about as much captan as rat blood.

d. Eukaryotic Microorganisms

Captan was examined in a point mutation assay using a haploid strain of Aspergillus nidulans (Bignami et al., 1977). 8-azaguanine resistant mutations were reported.

e. Mammalian cells in culture

Captan was used to treat cell cultures of V79-4 Chinese hamster lung fibroblasts (Arlett et al., 1975). Treatment with captan in suspension resulted in no absolute increase in the number of 8-azaguanine resistant colonies per plate. However, both the absolute number of ouabain resistant colonies and the number of variants per survivor were increased by captan at 5 and 10 ug/ml. Exposure to vapor from captan impregnated filter paper resulted in an increase in the number of both 8-azaguanine and ouabain resistant colonies.

2. DNA Damage [Data Summarized in Table 4]

DNA repair tests do not measure mutation per se , but DNA damage induced by chemical treatment of a cell. Microbial test systems measure this damage as cell killing. Mammalian cell systems - both in vitro and in vivo - measure the damage to DNA either directly, or as it is being repaired (DHEW, 1977).

Captan has been shown to cause DNA damage in bacteria, eukaryotic microoganisms, and in two mammalian cell lines.

Prokaryotic and Eukaryotic Microorganisms

This test is usually performed as a plate test with the chemical deposited in the center of a lawn of the E. coli or Salmonella typhimurium tester strains. The killing effects aremeasured as zones of bacteria growth inhibition and the ratio of the size of the zones between the normal and the repair-deficient strains is a measure of the differential killing effects. The test has also been performed by applying the test substance to one end of two or more streaks of indicator organisms on a single petri dish and looking for a differential shortening of the streaks. This allows for the simultaneous use of more than one type of repair-deficient strain on a single plate. This method has been used

with Bacilus subtilis and Saccharomyces cerevisiae

Mammalian cells synthesize DNA only during one stage of the cell cycle. This is referred to as "scheduled DNA synthesis." However, when the cellular DNA is damaged, repair synthesis can occur during the time when scheduled DNA synthesis is not taking place. This "unscheduled DNA synthesis" can be measured in synchronously growing cells as uptake of radioactive thymidine into the cell's DNA. It can be measured in cells in culture, or in meiotic and post-meiotic mouse spermatocytes in vitro (DHEW, 1977).

a. Bacteria

Captan was shown to cause differential killing of DNA repair deficient strains of the following bacteria: E. coli WP 2 and E. coli WP 2 uvrA (Bridges, B. A. et al., 1973), Bacillus subtilis H17 rec+/B. subtilis M45 rec- (Shirasu et al., 1976; Simmons, et al., 1977), and E. coli W311 polA+/ E. coli P3478 polA-(Simmons, et al., 1977).

b. Eukaryotic Microorganisms

Aspergillus nidulans, diploid strain P, was used for a mitotic segregation assay in which somatic crossing over was attributed to captan treatment (Bignami et al., 1977). R. Fahrig (1973) found gene conversion at two loci, ade 2 and trp 5, in Saccharomyces cerevisiae after treatment with captan.

c. Mammalian Cells in Culture

An SV-40 transformed human fibroblast cell line, VA-4, was treated with captan, with and without rat liver S-9 microsome fraction (Ahmed et al., 1977). A significant ($p<0.05$) increase in unscheduled DNA synthesis as measured by autoradiography was seen at all treatment levels. However, metabolic activation did not significantly alter the effect of captan.

Swenberg et al. (1976) found an increase in the rate of elution of single-stranded DNA from polyvinyl filters after lysing V79 Chinese hamster lung fibroblast cells treated with captan. No effect was seen when an S-9 microsomal fraction was added with the captan treatment. This indicates that captan can cause breaks in DNA.

3. Chromosomal Aberrations [Data Summarized in Table 5]

Chromosomal aberrations involve changes in number and structure and may include the loss or gain of entire chromosomes, chromosome breaks, nondisjunctions, and translocations. Tests for these abnormalities involve searching for chromosomal changes in somatic and germinal cells usually obtained from insects and mammals.

Chromosomal aberrations have been reported in two mammalian cell lines. Of the literature examined so far, in vivo tests (which are generally less sensitive than the in vitro tests) have not revealed significant indications of mutagenicity of captan with the exception of the dominant lethal test in Osborne-Mendel rats and CBA-J mice (Collins, 1972).

a. Mammalian Cells in Culture

Mammalian cells in culture can be employed for the assessment of chromosomal effects. Human cells, e.g. fibroblasts and lymphocytes, and Chinese hamster ovary cells with and without metabolic activation have been used. Gross chromosomal aberrations such as breaks, gaps, and rearrangements can be readily observed in these systems (DHEW, 1977).

A heteroploid human embroyonic lung cell line, L-132, and a line of rat-kangaroo cells were treated with captan (Legator et al., 1969). Mitosis and DNA synthesis were inhibited. A 36% increase over control levels in chromosome breaks was observed 2 hours after addition of captan at 10 ug/ml to the L-132 line. The increase was 41% at 4 to 5.5 hours and 14% at 24 hours after addition of captan. Infrequent exchange figures were also observed at 24 hours. In the rat-kangaroo line, captan also increased the frequency of cells with chromosome breaks, preferentially in the X chromosome. A dose-response effect was apparent.

Tezuka et al., 1978, treated diploid human fetus fibroblasts with captan at 0.5 to 4 ug/ml captan. Mitosis was inhibited at all dose levels and a dose-dependent increase in cells showing stickiness was seen, statistically significant ($p<0.001$) at the 3 and 4 ug/ml dosage levels. No increase in chromosome gaps or breaks were seen and the stickiness may not have been due to mutagenicity. Since the scoring method was not described, the usefulness of this study was limited.

The scoring criteria were not described for a cytogenetic analysis of bone marrow cell preparations from Wistar rats

Table 5

CHROMOSOMAL ABERRATIONS: IN VITRO CYTOGENETICS

| Reference | Assay | Organism | Results | Comments |
|---|---|---|---|---|
| Legator et al., 1969 | Cytogenetic | Human embryo lung cells | + | Dose related response in chromosome breaks. |
| | | Rat kangaroo cells | + | " " " |
| Tezuka et al., 1978 | Cytogenetic | Human fibroblasts | No increase in breaks or gaps. Stickiness dose response seen | Stickiness may not be related to mutagenicity |

CHROMOSOMAL ABERRATIONS: IN VIVO CYTOGENETICS

| | | | | |
|---|---|---|---|---|
| Tezuka et al., 1978 | Cytogenetic | Wister rats | - | |

CHROMOSOMAL ABERRATIONS: DOMINANT LETHAL IN RODENTS

| | | | |
|---|---|---|---|
| Collins, 1972 | Dominant lethal | Osborne-Mendel rats | + | |
| | " " | CBA - J mice | + | |
| Epstein et al., 1972 | " " | ICR/H2 Swiss mice | - | Relatively insensitive test |
| Kennedy, 1975 | " " | Charles River mice | | Not valid |
| Simmon et al., 1977 | " " | ICR/SIM mice | - | Dosed up to 5 g/kg/day. |
| Tezuka et al., 1978 | " " | C3H and SLC-ICR mice | | Not valid |

treated orally at single dose levels of 500, 1,000, or 2,000 mg/kg captan or five consecutive doses of 200, 400, or 800 mg/kg (Tezuka et.al., 1978). No chromosomal effects were reported.

There was a consistent, although statistically non-significant, increase in gaps but this may have been due to captan's binding to proteins rather than an effect on DNA.

b. Dominant Lethal Tests

Dominant lethal effects in the mouse or the rat seen as fetal wastage are consider to be indicators of chromosomal mutation produced in germinal cells by mutagenic substances (DHEW, 1977).

1) Collins Study

Dominant lethal effects attributable to captan were reported in Osborne-Mendel rats and CBA-J mice (Collins, 1972). Captan was given for 5 days by intraperitoneal injection in doses of 2.5, 5.0, and 10 mg/kg/day or by oral intubation in doses of 50, 100, and 200 mg/kg/day to groups of 15 rats and 15 mice. The rats were mated with one virgin female each week for the next 10 weeks. The mice were mated with two virgin females each week for 12 weeks. Caesarean sections were performed on the 13th day of pregnancy for the rats and on the 12th day for the mice.

a) Results in Rats

Significant increases ($p<0.05$) were found in the mean number of early deaths per pregnancy for those pregnancies sired by rats 4 weeks after the rats were given captan orally at a dose of 100 mg/kg/day. Increased early fetal deaths were also found in pregnancies sired by rats at 1, 2, and 5 weeks after treatment with 200 mg/kg/day captan.

When the litter was considered an experimental unit and affected litters were defined as those with at least one early fetal death, a significant increase ($p<0.05$) in the number of affected litters was seen in the rat test group given 100 mg/kg/day orally and mated after 4 weeks. The other two dose groups showed consistent increases in the numbers of affected litters. In addition, there were significant linear dose-response relationships in affected litters from rats mated 3 and 4 weeks after treatment.

When "affected litters" were defined as those with two or more early deaths, the data showed a significant increase ($p<0.05$) in the number of affected litters for rats given a daily oral dose of 100 mg/kg captan and mated 2 and 5 weeks later, and ($p<0.01$) for rats given a daily dose of 200 mg/kg captan, and mated 1, 2 and 5 weeks later.

b) Results in Mice

There were also significant increases ($p<0.05$) in the number of early fetal deaths per pregnancy among the potential offspring of mice given 200 mg/kg/day intraperitoneally and mated 4 and 5 weeks later. Similar increases in the number of early deaths per pregnancy were reported among the offspring of mice given 100 mg/kg/day and 200 mg/kg/day orally and mated 1 and 2 weeks later.

The groups of mice given captan at the highest doses showed significant increases ($p<0.01$) in the percentage of litters with 2 or more early fetal deaths for matings on week 5 after intraperitoneal administration and on week 1 for oral administration. Significant linear dose responses were seen for different weeks of mating for all combinations of species and routes: intraperitoneally treated rats mated in weeks 4 and 5; orally treated rats mated in weeks 1 and 2; intraperitoneally treated mice mated in weeks 1-3 and 5-7; and orally treated mice mated in weeks 1-5, 9, and 12.

2) Simmon Study

Captan, administered at up to 5,000 mg/kg/day in the diet for 7 weeks, did not increase the frequency of dominant lethal mutations in ICR/SIM mice (Simmon et al., 1977). The positive control was administered by intraperitoneal injection.

3) Epstein and Kennedy Studies

The following dominant lethal tests, although reporting no dominant lethal effects, are inconclusive as to whether captan may cause such an effect. Epstein et al., (1972) used ICR/Ha Swiss mice; however, the test was relatively insensitive (i.e. unable to detect small increased effects) since small group sizes were used and the dosages were low. The study performed by Kennedy (1975) also used a low dosage and additionally had no controls.

4) Tezuka Study

Tezuka et al., (1978) treated C3H and SLC-ICR mice with 5 daily doses of up to 600 mg/kg/day captan; however there were inconsistencies in reporting these observations. Consequently this study is also inconclusive as to whether captan may cause dominant lethal effects. For example, application of the formula given in the paper for calculation of the percentage of dominant-lethal mutations yielded results that differ from those reported. The protocol was not standard, using only a 6-week post-treatment mating period combined with a 2- to 4-day mating period. This regimen may have allowed the more active males to contribute more females to the experiment which may have biased the results.

c. Heritable Translocation Test

The heritable translocation test and the sex chromosome loss test have the capability of determining the heritability of chromosomal damage. These effects are measured in progeny of animals exposed to chemical mutagens. Thus, these assays can be employed not only as a means of detecting potential mutagens but also for the purpose of assessing risk (DHEW, 1977).

A heritable translocation test was performed by Stanford Research Institute (SRI) (project LSV-3493) for EPA (Simmon et al., 1977). Captan was administered in the diet for 8 weeks at levels of 2,500 ppm to 60 male ICR/SIM mice and 5,000 ppm to 61 male ICR/SIM mice. These males, the 60 negative control males, and the 66 triethylenemelamine-treated positive control males were mated with two females each, except for one low dose and one high dose male that were mated to only one female each. At maturity (10-12 weeks), 200 males were selected from each dose level group and mated to three females each. The females were sacrificed 14 days after mating and the uterine contents were examined for live and dead implants as an indication of sterility. A cytogenetic evaluation was made of meiotic cell preparations from the testes of those males suspected of being a translocate or non-breeder after two or three breedings. One translocation was found in the high dose group which would normally be sufficient to classify captan as positive for heritable translocations; however, one translocation was also seen in the negative control group.

This is the only heritable translocation found in over 1600 negative control males at SRI. This is an acceptable historical spontaneous background rate for heritable

translocations, however the presence of the event in this study makes it impossible to evaluate the significance of the heritable translocation in the captan-treated group. In order to resolve this issue it would be necessary to re-run this test, preferably using a larger number of animals.

C. Potential for Human Exposure

1. Introduction

The general population is exposed to captan by eating food which contains captan residues. In addition, agricultural workers, and occasionally bystanders, are exposed to much greater amounts of captan when they are present in fields during or after captan spraying. At present, the Agency has only limited data concerning human exposure to captan. Additional data is being sought, primarily through industry compliance with FIFRA Sec. 3(c)(2)(b) requests (Johnson, 1980), however data from any source is welcome. Until these data are available, Agency assessments of human exposure will be made on a "worst-case" basis.

2. General Population

a. Dietary Exposure

Captan is registered for use on a large number of food crops. Its use is extensive (Table 1) and there are a number of established tolerances for raw agricultural commodities (see Section I.B.2.) The Agency has calculated that a theoretical worst-case dietary exposure would be 0.117 mg of captan/kg of body weight per day[2/] (Table 6).

b. Nondietary (Dermal & Inhalation)

There are a number of nonagricultural uses of captan. Some of the treated products (e.g., wallpaper paste), are used in substantial amounts (Table 2) in or around domestic dwellings; therefore, people who live or work in areas where captan treated products are present may be exposed to captan residues.

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2/ This calculation was based on existing tolerances, the extent of crop treated (see Table 1), and an assumed average daily diet of 1.5 kg for a 60 kg person. However, the Agency anticipates that the actual levels of captan on treated crops will be much lower.

Table 6

Dietary "Worst Case" Exposure Calculations for Captan

| Food Commodity or Commodity Grouping | Food Factor (% diet) | Tolerance (ppm) | Percent of Crop Treated | Daily Intake (mg/1.5kg diet/day) |
|---|---|---|---|---|
| Almonds | 0.03 | 2.00 | 42.8 [1] | 0.00038 |
| Apples | 2.53 | 25.00 | 32.3 [1] | 0.30645 |
| Apricots | 0.11 | 50.00 | 21.0 [1] | 0.01733 |
| Avocados | 0.03 | 25.00 | 100.0 [2] | 0.01125 |
| Beans | 2.04 | 25.00 | 50.0 [3] | 0.38250 |
| Beet Greens | 0.03 | 100.00 | 10.0 [2] | 0.04500 |
| Beets | 0.17 | 2.00 | 100.0 [2] | 0.00510 |
| Blackberries | 0.03 | 25.00 | 100.0 [2] | 0.01125 |
| Blueberries | 0.03 | 25.00 | 100.0 [2] | 0.01125 |
| Broccoli | 0.10 | 2.00 | 50.0 [3] | 0.00150 |
| Brussel Sprouts | 0.03 | 2.00 | 50.0 [3] | 0.00045 |
| Cabbage, Sauerkraut | 0.74 | 2.00 | 100.0 [2] | 0.02220 |
| Cantalopes | 0.52 | 25.00 | 50.0 [3] | 0.09750 |
| Carrots | 0.48 | 2.00 | 50.0 [3] | 0.00720 |
| Cauliflower | 0.07 | 2.00 | 50.0 [3] | 0.00105 |
| Celery | 0.29 | 50.00 | 50.0 [1] | 0.10875 |
| Cherries | 0.10 | 100.00 | 13.8 [1] | 0.02070 |
| Collards | 0.08 | 2.00 | 50.0 [4] | 0.00120 |
| Corn, sweet | 1.43 | 2.00 | 50.0 [4] | 0.02145 |
| Cottonseed | 0.15 | 2.00 | 80.8 [2] | 0.00369 |
| Crabapples | 0.03 | 25.00 | 100.0 [3] | 0.01125 |
| Cranberries | 0.03 | 25.00 | 50.0 [2] | 0.01125 |
| Cucumbers, pickles | 0.73 | 25.00 | 100.0 [2] | 0.27375 |
| Dewberries | 0.03 | 25.00 | 100.0 [3] | 0.01125 |
| Eggplant | 0.03 | 25.00 | 50.0 [2] | 0.00563 |
| Garlic | 0.03 | 25.00 | 100.0 [3] | 0.01125 |
| Grapefruit | 0.99 | 25.00 | 50.0 [1] | 0.18563 |
| Grapes, raisins | 0.49 | 50.00 | 30.9 [3] | 0.11355 |
| Honeydew melons | 0.03 | 25.00 | 50.0 [2] | 0.00562 |
| Kale | 0.03 | 2.00 | 100.0 [2] | 0.00090 |
| Leeks | 0.03 | 50.00 | 100.0 [1] | 0.02250 |
| Lemons | 0.17 | 25.00 | 9.1 [1] | 0.00580 |
| Lettuce | 1.31 | 100.00 | 84.5 [1] | 1.66043 |
| Limes | 0.17 | 25.00 | 9.1 [2] | 0.00580 |
| Mangoes | 0.03 | 50.00 | 100.0 [2] | 0.02250 |
| Muskmelons | 0.03 | 25.00 | 100.0 [2] | 0.01125 |
| Mustard Greens | 0.06 | 2.00 | 100.0 [1] | 0.00180 |
| Nectarines | 0.03 | 50.00 | 21.0 [2] | 0.00473 |
| Onions (dry bulb) | 0.72 | 25.00 | 100.0 [2] | 0.27000 |
| Onions, green | 0.11 | 50.00 | 50.0 [2] | 0.04125 |
| Oranges | 2.17 | 25.00 | negligible [1] | 0.00000 |

Table 6 (Continued)

Dietary "Worst Case" Exposure Calculations for Captan

| Food Commodity or Commodity Grouping | Food Factor (% diet) | Tolerance (ppm) | Percent of Crop Treated | Daily Intake (mg/1.5kg diet/day) |
|---|---|---|---|---|
| Peaches | 0.90 | 50.00 | 21.0 1/ | 0.14175 |
| Pears | 0.26 | 25.00 | 5.5 1/ | 0.00536 |
| Peas | 0.69 | 2.00 | 50.0 3/ | 0.01035 |
| Peppers | 0.12 | 25.00 | 50.0 3/ | 0.02250 |
| Pimentos | 0.03 | 25.00 | 100.0 2/ | 0.01125 |
| Pineapple | 0.30 | 25.00 | 100.0 2/ | 0.11250 |
| Plums, Prunes | 0.13 | 50.00 | 17.3 1/ | 0.01686 |
| Potatoes | 5.43 | 25.00 | 66.4 4/ | 1.35207 |
| Pumpkin, Squash | 0.11 | 25.00 | 100.0 2/ | 0.04125 |
| Quinces | 0.03 | 25.00 | 100.0 2/ | 0.01125 |
| Raspberries | 0.03 | 25.00 | 100.0 2/ | 0.01125 |
| Rhubarb | 0.05 | 25.00 | 50.0 3/ | 0.00937 |
| Rutabagas | 0.03 | 2.00 | 100.0 2/ | 0.00090 |
| Shallots | 0.03 | 50.00 | 100.0 2/ | 0.02250 |
| Soybeans | 0.92 | 2.00 | 100.0 2/ | 0.02760 |
| Spinach | 0.05 | 100.00 | 100.0 2/ | 0.07500 |
| Strawberries | 0.18 | 25.00 | 100.0 1/ | 0.06750 |
| Summer Squash | 0.03 | 25.00 | 100.0 2/ | 0.01125 |
| Tangerines | 0.03 | 25.00 | 50.0 3/ | 0.00563 |
| Taro | 0.03 | 0.250 | 100.0 2/ | 0.00011 |
| Tomatoes | 2.87 | 25.00 | 71.1 1/ | 0.76539 |
| Turnips | 0.05 | 2.00 | 100.0 2/ | 0.00150 |
| Turnip Greens | 0.03 | 2.00 | 100.0 2/ | 0.00090 |
| Watermelon | 1.43 | 25.00 | 100.0 2/ | 0.53625 |
| TOTAL | | | | 7.013255 |

1/ Based on data as provided to EPA by registrants (Table 1).
2/ No usage data available, hence 100% assumed.
3/ Based on data estimates made by EPA (Table 2).
4/ Includes seed treatment useage which may not be relevant to dietary exposure

3. Workers

a. Agricultural

1) Applicators, Mixers, Loaders and Bystanders

a) Commercial

Michigan farm workers were studied (Oudibier et al. 1974) to determine the extent of their respiratory exposure to captan. These farmers used airblast speed sprayers drawn through the orchards by tractors. Personnel involved with the mixing and spraying procedures wore respirators equipped with filter pads and midget impingers containing ethylene glycol. The latter device was connected to a vacuum source and used to monitor pesticide levels in the breathing zone. After each spray operation the respirator pads and the impingers were analyzed for captan residues. The respirator pad analyses indicated that respiratory exposure was generally greater for mixers (0.8-1.9 µg/min) than sprayers (0.07-0.66 µg/min). Although no captan residues were found in the impinger samples the researchers reported difficulties with this sample collection methodology. A number of weaknesses in the published report were identified as follows: 1) No mention of the type of formulation used; 2) No recovery studies reported for the methodology used; 3) No indication of the dates of sample collection or the dates of the analyses; and 4) No detection limit given.

Captan exposure of farm workers in Maryland was studied (Hansen et al., 1978) during 16 separate orchard sprayings using a tractor-drawn, high-pressure sprayer equipped with a single-orifice handgun. Three men were involved in each spraying: the tractor driver, the sprayer operator and the observer. Following each spraying the exposure was determined from captan residues on respirator pads and patches attached to clothing and on orchard foliage.

The average dermal exposure was calculated to be 1.96 mg/person/hr with a maximum of 3.3 mg/person/hr. This was based on an assumed dermal exposed area of 0.294 $m^2$ when no protective clothing was worn. The amounts of captan residue collected from respirator pads of the tractor driver and sprayer operator averaged 0.032 mg/hr,

with the highest concentration sample obtained from any one worker being equivalent to 0.081 mg/hr. The urinalysis data were not reported. The captan residues on orchard foliage will be discussed under Section 2(a)(2).

b) Home Gardeners

The Agency is also concerned about possible exposure of home gardeners and orchard owners during application of captan. The Agency will solicit further information on this exposure in a FIFRA Section 3(c)(2)(B) letter to registrants.

2) Harvesters

Hansen et al. (1978) observed that captan residues on fruit diminish with time. The study found that the average captan residue on apples was 190 ppm at 4 hours following application, but then declined to 53 ppm after 14 days. Such information indicates residues of captan diminish following application, which shows that the period between application and reentry for harvesters may be of concern, as there is no established preharvest interval.

b. Nonagricultural

No information is available to the Agency for evaluating the occupational exposure potential from nonagricultural uses of captan (Table 2). The Agency requests such data in order to evaluate the likelihood of captan exposure to applicators, mixers, loaders and bystanders as well as to those who handle the treated materials.

## IV. OTHER RELEVANT ADVERSE EFFECTS

40 CFR Section 162.11(a)(3)(ii)(B) states that "a rebuttable presumption [that a notice of intent to cancel registration shall be issued] if a pesticide's ingredient(s), metabolite(s), or degradation product(s) ... produces any other [other than oncogenic or mutagenic effects] or delayed toxic effect in test animals at any dosage up to a level, as determined by the Adminstrator, which is substantially higher than that to which humans can reasonably be anticipated to be exposed, taking into account ample margins of safety."

Captan may produce other chronic or delayed toxic effects to organs and functions of the body including the lungs, central nervous system, hematopoietic system, metabolism, kidneys, reproductive systems and others. Currently available data strongly suggest that captan may have teratogenic, fetotoxic and hypersensitivity effects. The Agency is currently seeking more information on these issues. If, upon further evaluation of all the toxicity and exposure data the Agency determines that other such adverse effects are produced by exposure to captan at any level up to a level exceeding possible human exposure (taking into account ample margins of safety), then the Agency will issue a supplemental notice or notices of rebuttable presumption against registration (RPAR)(s).

In addition, a supplemental RPAR may be issued on any of the uses of captan which result in an acute hazard to aquatic species of wildlife as defined in 40 CFR Section 162.1(a)(3)(i)(B)(3).

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